

HARBERD et al -- Serial No.: 09/485,529

According to *In re Wands*, the test for enablement is not whether experimentation is necessary, but whether, if experimentation is necessary, it is undue.

In determining whether experimentation is undue, *In re Wands* sets out various factors that must be considered. For the reasons set out below, consideration of these factors shows any experimentation required by the skilled person in practicing the invention is not undue and the claims are, therefore, enabled.

a) *The nature of invention/scope of claims*

The claimed invention relates to isolated nucleic acid sequences that hybridize under highly stringent conditions with SEQ ID NO:14 and encode a growth inhibiting polypeptide. Claim 6 further recites part of the amino acid sequence of the encoded polypeptide and specifies that growth inhibition is gibberellin sensitive, while claim 14 specifies that growth inhibition is gibberellin insensitive.

The genus of nucleic acids covered by these claims is narrow and defined according to a close structural relationship to SEQ ID NO:14. The sequence of SEQ ID NO:14 thus defines and limits the structure of all the members of

HARBERD et al -- Serial No.: 09/485,529

the genus. The genus is further defined by the function of the polypeptide in inhibiting growth.

*b) Predictability of the art*

The Examiner asserts that it is unpredictable whether any and all polynucleotides of claims 6 and 14 would encode a polypeptide of the stated activity, and cites Broun et al and Lazar et al in support of this position.

However, both of these disclosures relate to specific subject matter that is distinct from that of the presently claimed invention. These disclosures do not constitute a general teaching that the effect on activity of modifying residues is inherently unpredictable.

Lazar et al teach that mutation of Asp47 and Leu48 of TGF $\alpha$  has various effects on activity, depending on the nature of the substitute residue. These residues are selected by the authors for mutation because they are conserved within the C terminus and apparently not important for overall conformation (p1248, col 1, last para). They are, therefore, mutated precisely because an effect on activity relative to wild type is anticipated (i.e., predicted) on the basis of primary sequence analysis. Such an effect is indeed observed at both residues. The conclusion drawn by a skilled person from the

HARBERD et al -- Serial No.: 09/485,529

paper is that it is possible to predict which residues are important in the activity of a polypeptide with little, if any, experimentation.

Broun et al teach that the extreme diversity of seed storage fatty acids is a consequence of the catalytic plasticity of the enzymes that synthesize these fatty acids. Firstly, it is clear that these enzymes represent a special case, and it is unusual for enzymes of different activities to be so closely related. There is nothing to suggest that this teaching can be extended to other proteins, especially those that do not produce a similarly complex and diverse product. Secondly, it is clear from page 131 that the authors were able to readily identify the seven residues responsible for activity by straightforward analysis of primary sequence. The importance of these residues was then confirmed experimentally. In other words, the residues that were responsible for activity were entirely predictable with little or no experimentation.

Residues conserved in the present polypeptides are indicated in Figure 10 and the specification provides further teachings about residues and motifs that are important for activity, in particular gibberellin responsiveness.

HARBERD et al -- Serial No.: 09/485,529

In the light of this teaching, it is clear that a skilled person can by and large predict whether a variant polypeptide will retain the activity of the wild-type polypeptide before undertaking any experimentation.

*c) Quantity of experimentation necessary*

The Examiner acknowledges that hybridization techniques and assays for testing whether a polypeptide has GA-responsive dwarfing activity would not require undue experimentation. However, making and testing all the polynucleotides encompassed by the claims is considered to represent an undue burden.

However, the mere repetition of techniques which are, in themselves, within the level of one skilled in the art, does not put those techniques beyond the level of one skilled in the art. If they are routine, they are routine and the skilled person can perform them any number of times without intellectual or creative input. It is noted that 'a considerable amount of experimentation is permissible, if it is merely routine.' (In re Wands).

Notwithstanding the above, the skilled person is not required to undertake an extensive synthesis and screening program covering every conceivable polynucleotide that might be encompassed by the claims. Given the narrow genus

HARBERD et al -- Serial No.: 09/485,529

of nucleic acids that hybridize to SEQ ID NO:14 under the stated highly stringent conditions, there is a reasonable expectation that most if not all hybridizing nucleic acids will have the stated activity. The skilled person will need to test very few hybridizing polynucleotides in order to identify a polynucleotide with the stated activity. The level of experimentation required to test these few polynucleotides using routine techniques is not undue.

*d) Relative skill of those in the art*

A person skilled in the field of plant molecular biology at the filing date would have a high level of skill and experience in the cloning and expression of plant genes and would be familiar with and experienced in all the techniques required to carry out the invention.

*e) Amount of guidance provided by the disclosure*

Contrary to the Examiners assertion, there is significant guidance in the specification for the skilled person to work the invention.

Variants and homologues of the sequence of Figure 3b are discussed in detail at page 17, line 7, to page 27, line 9. This passage teaches how to identify variant sequences, in terms of % homology, for example, using

HARBERD et al -- Serial No.: 09/485,529

sequence analysis software, and in terms of hybridization to the reference sequence under stringent conditions. The specification also provides guidance on how to test for activity of the sequence within the plant.

The directions provided by Applicants in the specification provide ample guidance to allow the skilled person to practice the invention as claimed.

*f) Existence of worked examples*

The specification describes the use of database screening to identify the rice EST D39460 and the subsequent screening of wheat and maize libraries using hybridization techniques to identify various clones of the wheat Rht and maize D8 loci. Wheat cDNA clones C15-1 and C15-10 and genomic clones 5a1 and 14a1 were shown to correspond to wheat Rht.

The cloning of these sequences allowed the analysis of dominant mutant alleles of D8 and Rht. Mutant loci from D8-1, D8-2023 and Rht -D1c were cloned and sequenced using PCR techniques and the lesions responsible for the dominant mutations characterized at the nucleotide level.

Not only have Applicants provided a number of worked examples of wild type clones from D8 and Rht but also at least three worked examples of cloned mutant sequences. A

HARBERD et al -- Serial No.: 09/485,529

skilled person would have no difficulty in following these examples to practice the present invention.

In summary, an analysis of the factors set out in *In re Wands* indicates that the claims 6, 14, 15 and 17-27 are fully enabled by the specification. Reconsideration of the rejection is respectfully requested.

Claims 6, 14, 15 and 17-27 stand rejected under 35 USC 112, first paragraph, as allegedly lacking written description. The rejection is traversed.

It is maintained that, for the reasons set out in the Amendment of July 8, 2002, one of skill in the art would conclude that Applicants were in possession of the claimed subject matter at the relevant date.

In response to this reasoning, the Examiner has argued that the state of the art teaches unpredictability is inherent in protein function so that not all sequences that hybridize under highly stringent conditions encode polypeptides of similar function. Lazar et al and Broun et al are cited in support of this position.

However, as described above, Lazar et al and Broun et al do not provide a general teaching of unpredictability but, in fact, indicate to the skilled person a significant level of predictability in the art.

HARBERD et al -- Serial No.: 09/485,529

As described above, Lazar et al teaches that the important residues in a sequence (e.g., Asp47 and Leu48 of TGF $\alpha$ ) can be readily identified with little or no experimentation, by sequence analysis. The finding that substitution at these residues affects activity, supports the initial observation that these residues are important. Broun et al relates to a highly plastic group of enzymes which synthesize an extremely diverse array of seed storage fatty acids. The residues responsible for the activity were again identified in the first instance by sequence analysis and then confirmed to be important by subsequent experimentation.

In practice, there is a significant degree of knowledge in the art about the relationship between the activity of a protein and its primary sequence. This allows important residues to be identified within a sequence and activities to be assigned to uncharacterized polypeptide sequences. The Lazar et al and Broun et al papers provide further evidence that the function of a polypeptide sequence is not inherently unpredictable.

Contrary to the Examiner's assertion, a person of skill in the art would, therefore, not expect substantial variation among species encompassed within the scope of these claims, given the high degree of structural



HARBERD et al -- Serial No.: 09/485,529

similarity that is required by the highly stringent hybridization conditions. The claims require a nucleic acid to encode a polypeptide that has an activity that is both specific and exemplified (growth inhibition) and an extremely high proportion of species within the genus would be expected to have this activity. Claim 6 further requires a specific sequence of residues that contribute to this activity, i.e., residues important to the activity are specifically recited.

Given the narrow genus covered by these claims and the level of skill and knowledge in the art, a representative number of species is disclosed, since the combination of highly stringent hybridization conditions, the coding function of DNA and the recited amino acid sequence are adequate to determine that Applicants were in possession of the claimed invention.

Claims 6, 14, 15 and 17-27, therefore, meet the written description requirement of 35 USC 112, first paragraph, and reconsideration is requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version With Markings To Show Changes Made."

HARBERD et al -- Serial No.: 09/485,529

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

**NIXON & VANDERHYE, P.C.**

By Mary J. Wilson  
Mary J. Wilson  
Reg. No. 32,955

MJW:tat

1100 North Glebe Road  
8<sup>th</sup> Floor  
Arlington, Virginia 22201-4714  
Telephone: (703) 816-4000  
Facsimile: (703) 816-4100

HARBERD et al -- Serial No.: 09/485,529

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE CLAIMS:**

6. (Thrice Amended) An isolated polynucleotide encoding a polypeptide which comprises the amino acid sequence DELLAALGYKVRASDMA (SEQ ID NO:104) and which on expression in a plant provides inhibition of growth of the plant, which inhibition is antagonised by gibberellin,

wherein said polynucleotide specifically hybridizes to the sequence of Figure 8A (SEQ ID NO: 14) at [42°C in 0.25M Na<sub>2</sub>HPO<sub>4</sub>, pH 7.2, 6.5% SDS, 10% dextran sulfate and a final wash at 55°C in 0.1X SSC, 0.1% SDS] 65°C in 0.25M Na<sub>2</sub>HPO<sub>4</sub>, pH 7.2, 6.5% SDS, 10% dextran sulphate and a final wash at 60°C in 0.1X SSC, 0.1% SDS.

10. (Twice Amended) An isolated polynucleotide according to claim [9] 6 wherein said polypeptide includes the amino acid sequence shown in Figure 9b (SEQ ID NO: 8) for the maize D8 polypeptide.

12. (Twice Amended) An isolated polynucleotide according to claim [9] 6 wherein said polypeptide includes the amino acid sequence shown in Figure 6b (SEQ ID NO: 5).

HARBERD et al -- Serial No.: 09/485,529

14. (Thrice Amended) An isolated polynucleotide encoding a polypeptide which on expression in a plant confers a phenotype on the plant which is gibberellin-unresponsive dwarfism or which on expression in a *rht* null mutant phenotype plant complements the *rht* null mutant phenotype, such *rht* null mutant phenotype being [resistance] resistant to the dwarfing effect of paclobutrazol,

wherein said polynucleotide specifically hybridizes to the polynucleotide sequence of Figure 8A (SEQ ID NO: 14) [at 42°C in 0.25M Na<sub>2</sub>HPO<sub>4</sub>, pH 7.2, 6.5% SDS, 10% dextran sulfate with a final wash at 55°C in 0.1X SSC, 0.1% SDS] under the following conditions: hybridization overnight at 65°C in 0.25M Na<sub>2</sub>HPO<sub>4</sub>, pH 7.2, 6.5% SDS, 10% dextran sulphate and a final wash at 60°C in 0.1X SSC, 0.1% SDS.

17. (Twice Amended) An isolated polynucleotide according to claim 15 wherein the polypeptide includes the amino acid sequence of a Rht polypeptide obtained from *Triticum aestivum*, with the amino acid sequence LNAPPPPLPPAPQ (SEQ ID NO:103) [is] deleted.

HARBERD et al -- Serial No.: 09/485,529

19. (Twice Amended) An isolated polynucleotide according to claim 18 wherein said one or more amino acids comprise the amino acid sequence DELLAALGYKVRSSDMA (SEQ ID NO: 106) [is deleted].

21. (Twice Amended) An isolated polynucleotide according to claim 18 wherein said one or more amino acids comprise the amino acid sequence VAQK (SEQ ID NO: 101) [is deleted].

22. (Twice Amended) An isolated polynucleotide according to claim 18 wherein said one or more amino acids comprise the amino acid sequence LATDTVHYNPSD (SEQ ID NO: 102) [is deleted].

24. (Twice Amended) An isolated polynucleotide according to claim 23 wherein said one or more amino acids comprise the amino acid sequence DELLAALGYKVRSSDMA (SEQ ID NO: 106) [deleted].

28. (Twice Amended) An isolated polynucleotide comprising [wherein a] the isolated polynucleotide according to claim 1 [is] operably linked to a regulatory sequence for expression.

HARBERD et al -- Serial No.: 09/485,529

32. (Thrice Amended) A nucleic acid vector [suitable] for transformation of a plant cell and including the polynucleotide according to claim 1.

33. (Thrice Amended) A host cell containing a heterologous polynucleotide or nucleic acid vector each comprising the isolated polynucleotide according to claim 1.

34. (Amended) A host cell according to claim 33 which is a microbial cell.

36. (Twice Amended) A plant cell according to claim 35 having said heterologous [said] polynucleotide in its genome.

39. (Twice Amended) A method of producing the host cell according to claim [33] 35, the method including incorporating said heterologous polynucleotide or nucleic acid vector into the cell by means of transformation.

40. (Twice Amended) The method according to claim 39 which includes recombining the polynucleotide with the

HARBERD et al -- Serial No.: 09/485,529

cell genome [nucleic acid] such that it is stably incorporated therein.

41. (Thrice Amended) The method according to claim 39 wherein said host cell is a plant cell and said method further includes regenerating a plant from one or more of said transformed cells.

44. (Twice Amended) A method of producing [a] the isolated plant, the method including incorporating a polynucleotide [or nucleic acid vector] according to claim 1 into a plant cell and regenerating a plant from said plant cell.

46. (Thrice Amended) A method of influencing the growth of a plant, the method including causing or allowing expression from a heterologous polynucleotide comprising the isolated polynucleotide according to claim 1 within cells of the plant,

whereby said expression of said heterologous polypeptide influences the growth of said plant.